SERUM FERRITIN LEVEL IN CONGENITAL CYANOTIC HEART DISEASE

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CERTIFICATE

This is certify that dissertation entitled "SERUM FERRITIN LEVEL IN CONGENITAL CYANOTIC HEART DISEASE" Submitted by Dr.SENTHILBABU to the Tamil Nadu Dr. M.G.R Medical University, Chennai, is in partial fulfillment of the requirement for the award of M.D Degree Branch – I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

This is consolidated report on **"SERUM FERRITIN LEVEL IN CONGENITAL CYANOTIC HEART DISEASE"** based on at Govt. Rajaji Hospital, Madurai, during the period octo 2004 to September 2006.

This is submitted to the **Tamilnadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the rules and regulations for the **M.D.** Degree Examination in General Medicine.

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CONTENTS

INTRODUCTION

Iron deficiency is the commonest cause of anemia not only in developing countries but also in developed world. Even in U.S.A, about 20% cases of anemia is attributed iron deficiency. In countries like India, the prevalence is even higher. Patients with cyanotic heart disease in whom the picture of erythrocytosis predominates are no exception. The red cell production depends on the availability of nutrients, including iron, vitamin B-12, folic acid and pyriodoxine. Iron plays a central role along with erythropoietin and committed stem cells in determining red cell production.

Anemia poses a special problem in patients with cyanotic congenital heart disease. It is an important risk factor for the cyanotic spells and cerebrovascular accident. It increase blood viscosity by its effect on the physical properties of red cells, relatively at a lower hematocrit level. At the same time the correction of anemia without monitoring the hematological parameters, may also cause an undue rise in hematocrit, worsening the situation.

To complicate issues further, the diagnosis of iron deficiency anemia is not possible clinically due to the association of erythrocytosis. The detection of anemia by hemoglobin or by hematocrit is also not accurate as both those

parameters will be elevated and hence the definition of anemia, as applicable to the general population can not be applied to those patients. Moreover, the iron deficiency anemia in patients with cyanotic congenital heart disease is more often a relative anemia. The term ‘relative iron deficiency anemia’ designates, an iron supply that would be adequate to meet the needs of basal erythropoiesis but which is not adequate to meet the needs of an expanded erythroid marrow. This leads to the nutritional deficiency.

Controversies exist in the diagnosis of iron deficiency in patients with cyanotic congenital heart disease. Automated equipments have increased the dependability of mean corpuscular volume, but with some limitations. Change take time to develop due to slow turnover of circulatory red cells, so that it will be possible to detect abnormalities only after the condition has been present for months.

Iron deficiency in a patient with cyanotic, heart disease plays a pivotal role since when it is uncorrected, it increases the risk of complications and when over enthusiastically corrected, it once again aggravates the complications. Now a days, the conservative approach is followed towards phlebotomy since it increases the risk of iron deficiency.

This study was conducted in order to estimate the incidence of iron deficiency in cyanotic heart disease patients in our hospital and to find out the best modality to detect it early in a polycythemic patient.

AIMS AND OBJECTIVES

- To assess Iron deficiency anemia in congenital cyanotic heart disease patients using serum ferritin levels as a sensitive index and to correlate other red cell indices with ferritin levels.
- To compare the red cell indices of cyanotic heart disease patients with that of normal population.

MATERIALS

SUBJECTS

All patients with established congenital cyanotic heart diseases attending Govt. Rajaji Hospital, Chennai between October 2004 – September 2006 formed the study group. Control group was formed by age and sex matched patient's attendants.

PERIOD OF STUDY

Two years

October 2004 to September 2006

ELIGIBILITY CRITERIA

1. Patients with established cyanotic heart disease over 12 year of age.
2. The disease must have been proved by all available modes of investigations.

Patients with any significant degree of infection were excluded from the study since serum ferritin level tend to be altered by infection.

Informed consent was obtained from patients and controls.

METHODOLOGY

Serum ferritin was assayed using pathozyme Ferritin Ref. OD 407 kit.

It is an enzyme immunoassay for the quantitative determination of ferritin in human serum.

Specific anti ferritin antibodies are coated on to microtitre wells. Test sera are applied. Then monoclonal anti-ferritin labeled with horse radish peroxidase enzyme is added. If human ferritin is present in the sample, it will combine with the antibody on the well and the enzyme conjugate resulting in ferritin molecule being sandwiched between the solid phase and enzyme linked antibodies. After incubation for about 45 minutes, the wells are washed with distilled water to remove unbounded labeled antibodies. On addition of substrate (TMB) a color will develop, indicating the presence of ferritin.

The absorbance is then measured at 450nm. The concentration of ferritin is directly proportional to the colour intensity of the test sample. This test has been calibrated against NIBSC-WHO – 80/602 human liver standard.

SERUM IRON AND TIBC MEASUREMENT

It was determined using iron and TBC kit from CREST biosystems (Ferrozine method).

PRINCIPLE

Iron, bound to transferring is released in acidic medium and ferric irons are reduced to ferrous irons. Fe^{++} reacts with ferrozine to form a violet colored complex.

The intensity of the complex formed is directly proportional to the amount of iron present in the sample.

Fe^{++} Acidic Medium → Fe^{++}

Fe^{++} + Ferrozine → violet coloured complex

TIBC

The serum is treated with excess ferrous to saturate the iron binding sites on transferring. The excess Fe^{++} is adsorbed and precipitated and the iron content in the supernatant is measured to give TIBC.

NORMAL VALUES OF PARAMETERS ASSESSED[45]

Parameter	Age (years)	Male	Female
Hb g%	10-17	12.5-16.1	12-15.0
	>18	13.5-18.0	12.5-16.0
Hct	10-17	36-47	35-45
	>18	45-52	37-47
MCV (fl)	10-17	78-95	78-95
	>18	78-100	78-100
MCH pg	10-17	26-32	26-32
	>18	27-31	27-31
MCHC		32-36	32-36
Serum Iron µg/dl		65-17.5	50-70
TIBC µg/dl		200 - 400	200-400
Sr. Ferritin ng/dl		20-300	15-120

REVIEW OF LITERATURE

Congenital cyanotic heart disease can be considered as a systemic disorder that affects haematological, respiratory, renal skeletal and central nervous system[20,32]. Haematological manifestations other than erythrocytosis include relative iron deficiency anemia, coagulation disorders and functional platelet disorders.

In the presence of marked right to left shunt since birth, as in cyanotic heart diseases there will be no normal postnatal fall of hemoglobin. The blood by passes the lungs and hence the oxygenation. The hypoxemic blood on reaching the kidney elicits erythropoietin response and plenty of erythropoietin is released. Erythropoietin stimulates the bone marrow to produce more red blood cells there by increasing the red cell count, hemoglobin and hematocrit[14,26].

The increase in red cells may cause increased oxygen carrying capacity of the blood. The blood volume is also increased due to increase in red blood cells. But at the same time plasma volume may get reduced. This reduces blood velocity. The stagnation of blood in the circulation causes tissue hypoxia which stimulates more and more erythropoietin and increased amount of red blood cells are produced inspite of a very high hematocrit.

Based on iron status of the body, cyanotic patients with erythrocytosis can be classified into two categories[19].

1. Compensated erythrocytosis in iron sufficient state.
2. Decompensated erythrocytosis in iron depleted state.

In iron sufficient state, patients with compensated erythrocytosis establish equilibrium hematocrit. Since iron is present in sufficient amount, haemoglobuin synthesis is enhanced and tissue oxygenation improves. Once a particular level of hematocrit is reached, the stimulus for erythropoietin secretion is removed and hematocrit will be stable. Symptoms of hyperviscocity are mild or absent if hematocrit is less than 65% when hematocrit $\geq$ 70% the symptoms are of moderate severity. Hence phlebotomy is rarely required.

Patients with decompensated erythrocytosis fail to achieve equilibrium. In this situation, tissue hypoxia stimulates erythropoietin secretion which in turn will stimulate the bone marrow to produce increased amount of red blood cells. But due to iron deficiency, sufficient amount of hemoglobin will not be produced and hence tissue hypoxia will not be eliminated. Hence the stimulus for erythropoietin persists and red blood cell production is uncontrolled. This further increases the hematocrit. These patients may have moderate to severe

symptoms due to hyperviscocity. In this situation, therapeutic phlebotomy is required frequently that further causes depletion of iron stores.

Causes of iron deficiency in congenital cyanotic heart disease

The following causes can be attributed to the presence of iron deficiency in cyanotic patients.

1. Dietary deficiency of iron is one of the most important cause of anemia in tropical countries. Appetite and absorption of nutrients are decreased in cyanotic patients.
2. The requirement of iron for proliferating red cells is increased i.e., the patient may have normal total body iron which may not be enough to cope up with excessive cell proliferation.
3. Repeated phlebotomies also reduce the iron stores but this is uncommon in our population.
4. Cyanotic heart disease patients have disturbances related to platelets and coagualtion cascade. They have decreased Factor, V, VII and fibrinogen. Hence, they have bleeding tendencies. Rarely, it may be severe enough to cause blood loss anemia.

Effects of iron deficiency

Iron deficiency decreases oxygen carrying capacity of blood. In patient with cyanotic heart disease, iron deficiency will further aggravate tissue hypoxia due to right to left shunt.

Iron deficient state also exacerbates cyanotic spells and metabolic acidosis.

Iron deficient red blood cells are rigid and resist deformation in microcirculation and elevates blood viscosity. This increases the risk of cerebrovascular accidents.

In iron replete state, cerebrovascular accidents are uncommon if hematocrit is less than 65%. But in iron deficient state, cerebrovascular accidents occur even if hematocrit is less than 65%[21].

According to Joseph K. Perloff symptoms of hyperviscosity occurring in patients with hematouril less than 65% are almost always due to iron deficiency[19]. Iron deficiency plays a crucial role in causing complications in patient with cyanotic heart disease. Simple iron deficient state without anemia is enough to aggravate complications. The correction of iron deficiency improves the quality of life in cyanotic patients.

The iron supplementation in iron deficient cyanotic heart disease patients must be closely monitored[19]. The hematocrit increases rapidly on iron supplementation. Correction with iron improves exercise tolerance, general well being and reduces attacks of cyanotic spells. The symptoms observed at low hemoglobin concentration tend to recur if hematocrit rises above 75%. Haematocrit measurement based on centrifugation technique causes plasma trapping and false elevation of hematocrit values. Hence, hematocrit must be measured in automated counters.

To find out the presence of anemia in a cyanotic patient with erythroytosis it is essential to know the sequence of events in deficiency before planning to investigate for anemia in a cyanotic heart disease patient. Sequence of events following iron deficiency.

There is an fall in hemosiderin content of liver and bone marrow followed by decrease in serum ferritin. Subsequently there is a fall in level of serum iron with increase in total iron binding capacity.

Free erythrocytic porphyrin increases and progressive hypochromia and microcystosis ensure. The actual iron containing enzymes are reduced as a last event. Variation in red cell size proceeds microcytosis in iron deficiency.

It may be probably due to addition of progressively smaller number of red cells in the peripheral blood as iron deficiency worsens.

Based on these facts iron deficiency can be classified into following categories[44].

1. Prelatent iron deficiency ‘or’ iron deplete state where there is no biochemical evidence of deficiency except a reduction in serum ferritin level. Physiologically there is an increased state of iron absorption.
2. Latent iron deficiency (or) iron deficiency without anemia. In this condition the iron stores are exhausted but the hemoglobin level is above the lower limit of normal, plasma iron is decreased and free erythrocytic protoporphyrin is elevated.
3. Early iron deficiency anemia where there is mid to moderate degree of anemia with normal red cell indices in some cells.
4. Late iron deficiency anemia where there is severe anemia with associated epithelial changes.

Experimentally induced iron deficiency anemia by phlebotomy causes no alteration in red cell indices except few abnormal cells in peripheral smear. The red cell distribution width is increased in early stages. Mean corpuscular

volume gets decreased (Bessman et al) and iron binding capacity will be increased. Finally epithelial changes occur.

This knowledge about the sequence of events of iron deficiency helps us to diagnose iron deficiency at an early stage even in cyanotic patient with erythrocytosis.

ELECTRONIC CELL COUNTERS

Red cell indices measured by red cell counters are reliable, reproducible and accurate.

Perloff et al, in 1989 categorically stated that estimation of hematocril in patients with cyanotic congenital heart disease must be based on automated blood cell counters.

Haematocrit measured by cytocentrifugation techniques shows a false elevation due to plasma trapping in between rigid iron deficient red blood cells.

Electronic counters measure complete blood count by means of two principles.

1. Electric Impedance
2. Light scatter

In impedance technique, the cells are passed through a small aperture to which an electric field has been applied. A small resistance is generated, which is measured as pulse height. Cells that do not follow a straight line through the field generate a bimodal pulse height. The cellular size is proportional to pulse height.

The red cell counters that use impedance technique measure MCV, hemoglobin and red blood cell country directly. MCH, hematocrit and MCHC are derived values.

The counters that use light scatter technique measure MCHC directly and hence MCHC measured by this instrument is more accurate.

RED CELL INDICES

Red cell indices are used in classification of anemia.

Mean corpuscular volume (MCV)

It represents the average volume of red cells. It is calculated from red cell count and hematocrit. But as previously discussed, in electronic counters using electric impedance technology, it is a directly measured index. It is expressed in femtoliters (fl). It is decreased in iron deficiency, anemia of chronic diseases, lead poisoning, thalaseemia and sideroblastic anemia.

It is increased in Vit B_{12} deficiency and folate deficiency.

Mean corpuscular Haemoglobin (MCH)

It represents the average weight of hemoglobin in each cell. It is calculated from hemoglobin and red cell count. It is expressed in picogram (Pg).

Mean corpuscular hemoglobin concentration (MCHC)

It is calculated from hemoglobin and hematocrit. It is expressed in percentage. The electronic counters using light scatter technique directly measure MCHC. It is increased in hereditary spherocytosis.

Investigations in a case of iron deficiency anemia in cyanotic heart disease

Since hemoglobin, hematocrit and red blood counts are elevated in cyanotic congenital heart disease we have to rely on other investigations.

Though there are battery of investigations in the diagnosis of iron deficiency anemia, they have their own pit falls.

During the first two decades of life there is hardly any stainable iron in the bone marrow. Hence staining for iron in bone marrow is of limited value in first two decades and it is an invasive procedure.

Serum iron is decreased well before other red cell indices to fall below the normal value. Serum iron level also decreases in inflammation and infection.

Total iron binding capacity and serum iron are used in calculating transferring saturation. A decrease in transferring saturation below 7% is diagnostic of iron deficiency. It is also decreased in malnutrition, infection, liver disease and nephritic syndrome.

Free erythrocytic protoporphyrin is a functional index of adequacy of iron delivery to the marrow. Porphyrin ring is formed in a developing red blood cell before incorporation of iron for heme. When there is iron deficiency free erythrocytic protoporphyrin level is increased. An increase of more than 3 microgram per gram is abnormal.

SERUM FERRITIN

Srum ferritin undergoes parallel changes in iron status. Its measurement depicts the storage iron pool[39,43]. It is reduced even if hemoglobin is normal and helps in early detection of iron deficiency. In acute and chronic inflammation serum iron is shifted to storage sites and hence ferritin is increased. Increase inferritin level is seen in many condition. But decrease the ferritin level is seen only in iron deficiency anemia.

THERAPEUTIC TRIAL

It is a well known fact that the determination of hemoglobin response to3-4 weeks of iron is the most sensitive and conclusive test for detection of subclinical iron deficiency. It was considered as the gold standard in the diagnosis of early iron deficiency anemia. A rise of hemoglobin by 1-2g% within three to four weeks of iron supplementation is an evidence of early iron deficiency. But the response depends upon the patient's compliance and hence there is every chance of bias. Moreover in cyanotic congenital heart disease, iron supplementation must be closely monitored. Iron has to be given at a lower dosage, as hematocrit will rapidly rise following the correction of deficiency. Hence, it is not ideal to try this methods in such a population with erythrocytosis. Hence in such cases measurement of red cell indices reveal the presence of early iron deficiency anemia.

INCIDENCE OF ANEMIA IN CYANOTIC PATIENTS

Taussing found that levels of hemoglobin in the range of 10-13%g might constitute anemia in cyanotic heart disease. Similarly Haga et al[15], postulated that hemoglobin and hematocrit of normal range might constitute anemia in patients with cyanotic heart disease and suggested that measurement of MCV, MCH and serum ferritin was required to diagnose iron deficiency anemia.

Drossons C et al[25], studied this red cell indices are serum ferritin of cyanotic heart disease patient and found that MCHC was a convenient index of iron deficiency anemia.

Guha et al, studied 33 cases of cyanotic heart disease patients for iron deficiency. They correlated red cell indices – mean corpuscular volume, mean corpuscular hemoglobin with serum iron and iron binding capacity. They concluded that symptoms of hyperviscosity manifested in iron deficiency patients at a level of hematocrit lower than that known to produce symptoms. They also concluded that low dose iron therapy was effective in relieving symptoms of hyperviscosity.

Nageswara Rao et al (1994)[4] studied 32 children with cyanotic heart diseases for iron deficiency and concluded red cell indices help in early diagnosis of iron deficiency anemia.

CEREBROVASCULAR ACCIDENTS

Cerebrovascular accidents are common in cyanotic heart disease patients due to erythrocytosis. Tyler and Clark found that cerebrovascular accidents occur in 3.8% patients of congenial heart disease and among them 14.5% occur in congenital cyanotic heart disease patients.

Phornphutkul et al[32] concluded that a majority of cerebrovascular accidents occur in less than 2 years of age and about 70% episodes occur in less than 4 years of age. They attributed anemia and hypoxia to cerebrovascular accidents in less than 2 years of age. The anemia decreases the deformability of red blood cells and hence these cells increase the blood viscosity in microcirculation at a lower hematocrit thereby leading to vascular occlusion. As per their observations 90% of cerebrovascular accident occur in patients with transposition of Great arteries and Tetrology of Fallot.

Linder Kamp et al[24], found that hemoglobin concentration more than 20%g is associated with increased risk of thromboembolic episodes.

Ammash et al[1] in 1996 studied adult patients with cyanotic heart disease. They concluded that incidence of cerebrovascular accidents are very high in patients with microcytosis with statistical significance ($p<0.05$).

OBSERVATIONS

35 patients with cyanotic heart disease were studied for the presence of anemia. Parameters like hemoglobin, haematocrit, red blood cell count, serum ferritin, serum iron and total iron finding capacity were estimated. Mean corpuscular volume, mean corpuscular heamglobin and mean corpuscular hemoglobin concentration were estimated. These red cell indices were also measured for control population of similar age group. The following observations were made.

Table 1

Age - Sex Distribution

Age in years	**Cyanotic n = 35**		**Control n=25**	
	Male	**Female**	**Male**	**Female**
11-15	6	5	4	4
16-20	7	4	5	2
21-25	6	0	3	0
26-30	2	0	2	1
31-35	2	0	1	0
>35	1	2	2	1
Total	24	11	17	8

It was observed that the Male : Female ratio in the study group and the control group was 2.18:1 and 2.12:1 respectively.

SEX GROUP CROSS TABULATION

Table 2

Sex	Group		Total
	Study	Control	
Male	24	17	41
Female	11	8	19
Total	35	25	60

$X^2 \rightarrow 0.02$

P=0.96 (not significant)

Table 3

Group	Total	Mean age	S.D.	K test
Study	35	20.77	8.738	T=0.11
Control	25	20.52	8.352	P = 91

(Not significant)

There was no significant difference in age and sex between study and control group.

Table 4

Incidence of Iron depleted state

	Serum Ferritin < 20mg/dl	**Serum Ferritin >20mg/dl**	**Total**	**%**
Study	26	9	35	74
Control	11	14	25	14

X^2 = 5.66 % in study group – 74%

P = 0.02% in control group – 44%

It was observed that the iron depleted state was more common in cyanotic patients and it was statistically significant.

Table 5

Distribution of Hemoglobin

Hb in gm	**Study group**	**Control group**
<10	0	10
10-12	2	10
12-14	10	5
14-16	17	0
>16	6	0

The hemoglobin of the study group varied between 11.5g to 16.8g%, while in the control group it was between 8.9g% to 13.5g%.

20 patients were anemic in the control population based on hemoglobin where as only 5 had hemoglobin in anemic range in the study population.

Table 6

Distribution of Haemotocrit

Hct%	Study group	Control group
<30	0	10
30-36	2	10
36.1-42	10	5
42.1-48	17	0
48.1-50	6	0

The haematocrit varied from 35-50% in study group where as it was between 25.5% to 40.5% in the control group.

19 patients were anemic in control population based on haemotoric where as only 4 had haematocrit in anemic range in study group.

Table 7

Distribution of MCV

MCV (fl)	Study group n=35	Control group n=25
<65	0	2
65.1-70	3	2
71.1-75	8	4
75.1-80	20	4
81.1-85	3	7
>85.1	1	5

The MCV varied between 67.1 fl to 92.0 in study group. It was between 64.3 and 97.6 in control group.

Table 8

Red cell parameters in relation to sex

STUDY GROUP

Parameter	Male		Female	
	Mean	**S.D.**	**Mean**	**S.D.**
Hb g%	14.78	1.35	13.92	1.50
PCV %	44.43	4.20	41.73	4.56
MCV fl	76.38	3.84	76.40	6.39
MCH pg/ cell	25.31	1.17	23.35	2.25
MCHC g/dl	33.33	0.69	33.35	0.43
RBC million /cumm	5.86	0.62	5.48	0.76
Sr. Iron µg/dl	47.96	40.06	42.82	38.98
TIBC µg/dl	413.33	97.38	394.45	115.63
Sr. ferritin ng/dl	20.88	17.07	18.55	18.22

Serum iron was significantly lower and TIBC was significantly elevated in females when compared to males.

Table 9

Red cell parameters in relation to sex

CONTROL GROUP

Parameter	Male		Female	
	Mean	**S.D.**	**Mean**	**S.D.**
Hb g%	10.88	1.49	10.14	1.68
PCV %	32.63	4.47	30.45	5.00
MCV fl	80.22	9.62	77.75	6.51
MCH pg/ cell	26.77	3.20	25.94	2.16
MCHC g/dl	34.80	0.62	34.30	0.82
RBC million /cumm	4.07	0.35	4.01	0.59
Sr. Iron µg/dl	77.94	28.89	54.38	26.52
TIBC µg/dl	298.82	82.79	365.63	92.00
Sr. ferritin ng/dl	69.94	46.39	44.63	50.76

Mean of serum iron serum ferritin significantly lowered and TIBC was significantly elevated in females when compared to males.

COMPARISON OF RED CELL INDICES IN VARIOUS SUBSETS OF PATIENTS AND CONTROLS

Hemoglobin (g%)

Table 10-A

Study	Control
14.51±1.44	10.64±1.56
	P = 0.001

The hemoglobin was significantly elevated in study group.

Table 10-B

CCHD	Eisenmenger
14.55±1.42	14.41±1.56
	P=0.79

There was no significant difference between the both groups.

Table 10-C

Iron depleted state		Iron sufficient state	
Study	**Control**	**Study**	**Control**
14.44±1.54	9.17±0.49	14.72±1.33	11.79±1.02
P=0.001		P=0.001	

The hemoglobin levels observed between study and control groups in both iron depleted and iron sufficient states were statistically significant and it was elevated in study group.

Table 10-D

Cyanotic Population

Iron depleted state	Iron sufficient state
14.44±1.54	14.72±1.33

There was no significant difference in hemoglobin values between iron depleted and iron sufficient states.

PACKED CELL VOLUME (%)

Table 11-A

Study	Control
43.58±4.43	31.93±4.66

P = 0.001

The PCV observed in cyanotic patients was significantly higher than normal population.

Table 11-B

CCHD	Eisenmenger
43.77±4.35	43.10±1.56

P = 0.69

There was no significant difference among the above groups regarding PCV values.

Table 11- C

Iron depleted state		Iron sufficient state	
Study	**Control**	**Study**	**Control**
43.38±4.46	27.55±1.44	44.13±3.50	35.38±3.06
P=0.001		P=0.001	

PCV, irrespective of the iron status was significantly elevated in the cyanotic population.

Table 11- D

Cyanotic population

Iron depleted state	Iron sufficient state
43.38±4.76	44.13±3.50

PCV showed no significant different in the above group.

Mean Corpuscular Volume (fl)

Table 12-A

Study	Control
76.38±4.69	79.43±8.69

P = 0.09

There was no statistical difference in MCV among the cyanotic and control population.

Table 12-B

CCHD	Eisenmenger
75.63±4.26	78.27±5.11
	P=0.014

MCV showed no significant difference among the above group.

Table 12-C

Iron depleted state		Iron sufficient state	
Study	**Control**	**Study**	**Control**
76.00±4.86	73.78±6.24	77.47±4.23	83.86±7.82
P=0.25		P=0.04	

MCV was significantly reduced in cyanotic population of iron sufficient group but no significant difference was noted in iron depleted state. .

Table 12-D

Cyanotic Population

Iron depleted state	Iron sufficient state
76.00±4.86	77.47±4.23

No significant difference was observed between the above groups.

MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION

Table 13-A

Cyanotic	Control
33.37±0.62	34.36±0.62
	P = 0.57

There was no significant difference observed in MCHC of both groups.

Table 13-B

CCHD	Eisenmenger
33.26±0.48	33.64±0.84
	P = 0.10

There was insignificant difference in the value of MCHC in above groups.

Table 13- C

Iron depleted state		Iron sufficient state	
Study	**Control**	**Study**	**Control**
33.37±0.69	34.80±0.62	33.37±0.36	33.80±0.62
P=0.73		P=0.49	

No difference was observed in iron deplete andiron sufficient group.

Table 11- D

Cyanotic population

Iron depleted state	Iron sufficient state
33.37±0.69	33.37±0.36

No statistical difference was noted in MCHC in above group.

RBC COUNT

Table 14-A

Cyanotic	Control
5.74±0.68	4.04±0.43

P = 0.001

RBC count was significantly elevated in cyanotic patients.

Table 14-B

CCHD	Eisenmenger
5.84±0.63	5.51±0.76

No significant difference was observed in RBC count between CCHD and Eisenmenger.

Table 14- C

Iron depleted state		**Iron sufficient state**	
Study	**Control**	**Study**	**Control**
5.73±0.68	3.83±0.49	5.80±0.71	4.23±0.33
P=0.001		P=0.001	

The RBC count was significantly decreased in cyanotic population of both iron depleted and iron sufficient state.

Table 11- D

Cyanotic population

Iron depleted state	**Iron sufficient state**
5.73±0.66	5.80±0.71

There was no significant difference observed in RBC count among iron sufficient and iron depiction cyanotic patients.

MEAN CORPUSCULAR HEMOGLOBIN

Table 15-A

Study	Control
25.33±1.55	26.50±2.89

P = 0.05

There was no statistical difference in MCH in cyanotic and control population.

Table 15-B

CCHD	Eisenmenger
24.95±1.26	25.27±1.88

P = 0.09

There was no difference in MCH values between the above group.

Table 15- C

Iron depleted state		Iron sufficient state	
Study	**Control**	**Study**	**Control**
25.24±1.68	24.6±2.10	5.58±1.54	28±2.58
P=0.033		P=0.02	

In iron sufficient group, there was no significant reduction in MCH in cyanotic population.

Table 15- D

Cyanotic population

Iron depleted state	Iron sufficient state
25.24±1.68	25.58±1.54

There was no significant difference in MCH in the above group.

SERUM IRON

Table 16-A

Study	Control
46.34±39.64	70.40±29.79

P = 0.01

The serum iron was elevated in control population which was statistically significant.

Table 16-B

CCHD	Eisenmenger
49.68±41.01	39.50±37.12

P = 0.53

There was no significant difference observed in above two groups.

Table 16- C

Iron depleted state		Iron sufficient state	
Study	**Control**	**Study**	**Control**
29.96±8.70	40.0±6.33	102.33±41.14	94.29±14.53
P=0.001		P=0.51	

Serum iron was significantly lowered in cyanotic population of iron depleted state. This difference was not significant in iron sufficient state.

Table 16- D

Cyanotic population

Iron depleted state	Iron sufficient state
29.96±8.70	102.33±41.14

Serum iron was significantly reduced in anemic population of cyanotic group.

TIBC

Table 17-A

Study	Control
407.40±102.11	320.20±89.75

P = 0.001

There was a significant increase in iron binding capacity in cyanotic patients.

Table 17-B

CCHD	Eisenmenger
493.16±103.49	418.0±103.18

P = 0.70

The TIBC in both groups were increased but this showed no statistical significant.

Table 17- C

Iron depleted state		Iron sufficient state	
Study	**Control**	**Study**	**Control**
451.92±65.16	399.55±59.46	278.78±77.36	256.86±51.36
P=0.03		P=0.44	

The TIBC value was significantly elevated in cyanotic patients of iron depleted population. Though this value was elevated in iron sufficient patients with cyanotic the amount of elevation was significant.

Table 17- D

Cyanotic population

Iron depleted state	Iron sufficient state
451.92±65.16	278.78±77.36

TIBC was significantly elevated in iron-depleted state of cyanotic population.

SERUM FERRITIN

Table 18-A

Study	Control
20.77±17.17	61.84±48.29

P = 0.001

Serum ferritin was significantly lowered in cyanotic patients.

Table 18-B

CCHD	Eisenmenger
20.56±16.41	21.30±19.88

P = 0.91

There was no significant difference in ferritin levels among the above groups.

PARAMETERS IN PATIENTS WITH CONGESTIVE CARDIAC FAILURE

Table 19

Parameter	Mean	SD
Hb g%	12.9	0.8
PCV %	41.3	3.2
MCV fl	68.9	1.5
Sr. Ferritin ng/dl	8.25	1.10

n=3

The incidence of congestive cardiac failure was 8% in our study. The mean ferritin and MCV was significantly reduced in patients with congestive cardiac failure when compared to others in cyanotic group.

DISCUSSION

The observations made in respect of hemoglobin (Hb), hematocrit (Hct) Red Blood Cell (RBC count), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemologbin Concentration (MCHC), serum iron, serum ferritin, Total Iron Binding Capacity (TIBC) were analysed and following inferences were drawn.

AGE DISTRIBUTION

Study population comprised of 22 patients in the age group of 11-20 years, 10 between 20-30 years of age and 5 were above 30 years. The control population comprised of 15 in age group between 11-20 years, 6 between 20-30 years of age and 4 were above 30 years. The control group matched with the study group in respect to age distribution.

SEX DISTRIBUTION

There were 24 males and 11 females in the study group. The control group comprised of 17 males and 8 females. The male : female ratio in study group was 2.18:1 and in control group was 2.12:1. The control group matched with the study group in respect to sex.

DISTRIBUTION OF HEART DISEASES IN STUDY POPULATION

14 patients had tetrology of fallot, 10 were suffering from Eisenmenger syndrome 3 had double outlet right ventricle, 2 had total anomalous pulmonary venous communication, 2 had transposition of great arteries. We had one each with truncus arteriosus, Ebstein's anomaly, pulmonary AV malformation and tricuspid atresia.

HAEMOGLOBIN

The hemoglobin in the cyanotic group varied between 11.5g% to 16.8g%. In the control group it was between 8.9g% to 13.g%. Only five patients were considered anemic when hemoglobin alone was taken as a out off point in the study group. 20 patients were anemic in the control group.

The mean hemoglobin of study population was 14.51± 1.44g%. It was 10.04±1.56g% in the control population. The hemoglobin was significantly elevated in the study group. Though the hemoglobin values were lower in females than in males in the cyanotic population, this was not significant. As discussed previously, the chronic cyanotic state stimulates erythropoietin production from kidneys and bone marrow is stimulated thereby the hemoglobin levels in cyanotic population is elevated. Hence hemoglobin was not considered as a sensitive marker of anemia in cyanotic patients.

The hemoglobin level of our patients correlated well with that observed by others.

Table 20-A

Study Population

Parameter	Present study	Nagaswara Rao et al
Hb	14.51±1.44	14.25±1.32

Table 20-B

Parameter	Iron depleted state		Iron sufficient steate	
	Present study	Nagaswara Rao et al	Present study	Nagaswara Rao et al
Hb	14.44±1.54	15.77±3.17	14.72±1.33	14.04±2.05

There was no significant differences in the levels of hemoglobin among iron depleted state and iron sufficient population of cyanotic patients.

PACKED CELL VOLUME (HEMETOCRIT)

The mean hemetocrit varied from 35-50% in the cyanotic group where as it was between 25.5-40.5% in the control group.

The mean hemetocrit was 43.58±4.42 in the cyanotic patients with was significantly higher than that observed in control population. Only four patients fell into anemic group in cyanotic population based on hematocrit alone. It was safely inferred that hematocrit is not a sensitive marker of

anemia in cyanotic patients. The elevated values in cyanotic patients was attributed to chronic hypoxemic state.

Table 21

Cyanotic Patient

Parameter	Present study	Nagaswara Rao et al
Hct	43.58±4.43	46.75±3.85

The values observed in our study were similar to that observed by others.

RED BLOOD CELL COUNT

The mean RBC count in the study group was $5.74\pm0.68 \times 10^{12}$ and this was significantly elevated that that of the control group. This may be attributed to the increased erythropoietin level that stimulates bone marrow to produce more RBCs. Our study correlated well with those conducted by others.

Table 22

Parameter	Present study	Nagaswara Rao et al
RBC count	5.74±0.68	6.06±1.53

None in the study group was considered anemic based on RBC count. Hence RBC count was considered as an insensitive marker of anemia in cyanotic heart disease.

MEAN CORPUSCULAR VOLUME

The MCV varied between 67.1 fl to 92.0 fl in the study group. It was between 64.3 fl and 97.0 fl in the control group.

The mean corpuscular volume in cyanotic population was 76.38±4.66 fl. The MCV was decreased in cyanotic population but this decrease in absolute value was insignificant. Since there was no statistical significance, the cutoff value of MCV to define anemia will be similar to that of normal population.

21 of our cyanotic patients was considered anemic based MCV value alone. Since 26 of our patients were in iron depleted state and MCV detected most of them, it can be considered as a sensitive marker of anemia.

This observation is in line with that observed by Sami Ulus et al who observed that 23 of his patients with decreased MCV values among 28 of iron depleted cyanotic patients.

Table 23

	Present study	**Sami Ulus et al**
Patient with decreased MCV	21	23

The mean corpuscular hemoglobin in the cyanotic group was 25.33±1.55 and in the control population it was 26.50±2.89. This reduction

was statistically significant. 20 of the cyanotic patients were anemic based on MCH values. Though MCH correlated well with MCV, the latter was more reliable indicator of anemia since MCH was a derived value.

Sami Ulus et al and Haga P et al (1993) observed that both MCV, MCH revealed iron deficiency in cyanotic heart disease which were in line with our study.

MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION (MCHC)

The mean of MCHC of cyanotic group was 33.37±0.62 and the mean of control group was 34.46±0.62. There was no statistical significant between the means of MCHC in both group.

This was similar to that observed by Nagaswara Rao et al.

Table 24

Present study	Nagaswara Rao et al
33.37±0.62	31.99±1.55

All of our patients had MCHC within normal limits.

MCHC depends on hemoglobin and hemotocrit. In iron deficiency anemia both hemoglobin and hemetocrit are reduced and hence the ratio remains unchanged. This explains the normal values observed in our patients.

Moreover in electronic cell countries, using electric impedance technology, MCHC will be a derived value and hence less reliable.

In our study, MCHC was lower in cyanotic population. Denis Miller observed that hematocrit need not fall in parallel to hemoglobin in all cases. Resove and Joseph K. Perloff studied the hematological parameters of 40 adults with cyanotic congenital heart disease and reported that a subset of patients had an unstable hemetocrit that rose frequently. Those patients with unstable hematocrit were iron deficient when compared to others. The authors came to a conclusion that iron deficiency in cyanotic patients caused an adaptive failure and these patients show an excessive erythroid response. Hence their hematocrit will be elevated unlike the usual fall in iron deficiency. Since hematocrit forms the denominator in the calculation of MCHC, any increase in hematocrit reduces MCHC. This explains the lower levels of MCHC observed in our patients.

David Bessman and Edward Custner studied the hematological values in 13 polycythemic patients. They observed that MCHC fell by only 0.5% whereas other hematological indices showed a dramatic fall well ahead of MCHC. Hence MCHC from our study was not a sensitive indicator to diagnose anemia in cyanotic patient.

SERUM IRON

The mean serum iron in the cyanotic population was 46.34±39.64. The control population had their mean as 70.40±29.79. The serum iron was reduced significantly in cyanotic population. 24 of our 35 patients had iron levels lower than the normal values. Drosses et al., studied 38 patients of cyanotic heart diseases. 37.5% of his cyanotic population had low level of serum iron.

Table 25

	Present study n=35	**Drosses et al n=38**
% of population with low serum iron	66%	37.5%

In our study 66% of cyanotic population had low level of serum iron.

This difference can be attributed to the high prevalence of nutritional deficiency anemia (especially Fe) and chronic hook worm infestation in our population.

TOTAL IRON BINDING CAPACITY

TIBC was estimated in both cyanotic and control group. The means of TIBC in cyanotic and control group were 407.40±102.11 and 320.20±89.75 respectively. The total iron binding capacity in the cyanotic population was markedly elevated. This difference was statistically significant 24 patients in

cyanotic population had elevated values and this correlated well with the serum iron values. TIBC had an inverse relationship with that of serum iron values.

SERUM FERRITIN

Serum ferritin, the storage form of iron, was estimated in our control and cyanotic population. The mean in cyanotic population was 20.77±17.17 and the mean of serum ferritin in control population was 61.84±48.29. The cyanotic population had reduced levels of serum ferritin. This reduction was statistically significant. 26 of our cyanotic patients had low serum ferritin levels, that accounted for 74% of our cyanotic population. In the control population 44% had reduced serum ferritin levels.

Table 26

	Iron depleted state	**Iron sufficient population**	**% of iron depleted population**
Cyanotic	26	9	74%
Control	11	14	44%

P=0.02

This iron depleted state was found to be more common in cyanotic population and this was statistically significant.

The increased incidence of iron depleted state in cyanotic population can be attributed to the

i) Increased prevalence of iron deficiency anemia in general population.

ii) Chronic hypoxia in cyanotic state causes an augmented erythropoietin response which inturn leads to increase utilisation of iron by the expanded bone marrow.

iii) Bleeding disorders seen in cyanotic heart diseases patient.

Serum ferritin was found to be increased in conditions like acute infectious, inflammation iron overload state. But decreased ferritin was noted only in iron deficiency state. In our study ferritin emerged to be a sensitive indicator of iron deficiency which was also observed by Haga et al.

Table 27

Comparison of iron deplete state with other studies

Group	**Iron depleted state**
Sami Ulas et al n=44	62.6
Gaiha et al n=33	18.2
Present study n=25	74

This variation in iron depleted state can be attributed to the varying prevalence of iron deficiency anemia in general population.

Comparison of parameters between congenital cyanotic heart disease and Eisenmenger syndrome

We had 10 patients with Eisenmenger syndrome and 25 patients with congenital cyanotic heart disease. The hematological parameters and the iron stores were compared between the congenital cyanotic heart disease and the Eisenmenger syndrome. It was inferred that there was no significant difference in the red cell of parameters and iron stores. The nature of cardiac disease had no effect on the anemic states. The cyanotic state which was common manifestation of the above two conditions that determined the severity of anemia.

Comparison of variables among iron depleted and iron sufficient patients

Serum iron was significantly lower and TIBC was significantly higher in iron depleted cyanotic population when compared to iron sufficient cyanotic population.

The means of other red cell indices were not statistically significant.

Comparison of variables between cyanotic and control group

Hb, PCV, RBC count were significantly elevated in the cyanotic population which can be explained by increased erythroid response to chronic hypoxemia in this subgroup.

Serum iron and serum ferritin were significantly lowered in cyanotic population.

SEX DIFFERENCE IN RED CELL INDICES

Neither cyanotic nor the control population showed any significant difference in red cell induces among the both sexes.

Female cyanotic patients significantly differed from males only in serum iron and TIBC.

Table29 – Cyanotic

Parameter	Female	Male
Serum iron	42.82±38.98	47.96±40.66
TIBC	349.45±115.63	413.33±97.38

Similar trend was observed in control population as well.

Table 30 – Control

Parameter	Female	Male
Serum iron	54.38±26.52	77.94±28.29
TIBC	365.63±92.10	298.82±82.79
Serum ferritin	44.63±50.76	69.94±46.39

This could be explained by the increased prevalence of iron deficiency state in female population.

CONGESTIVE CARDIAC FAILURE

We had 3 patients with congestive cardiac failure. The incidence was 8%. Two were diagnosed to have TOF and one had TGA. All had low MCV and very low serum feritin levels.

Parameter	CCF	Cyanotic patients
Hb g%	12.9±0.8	14.78±1.35
PCV	41.3±3.2	44.43±4.20
MCV fl	68.3±1.5	76.38±3.84
Srum Ferritin ng/dl	8.25±1.10	20.88±17.02

The parameters were significantly decreased in cyanotic patients with congestive cardiac failure. This fact can be explained that severe anemia aggravates failure. Since we had only 3 patients, this requires a larger study to confirm the report.

CONCLUSION AND SUMMARY

- 35 patients were analysed for iron deficiency anemia in congenital cyanotic heart disease.
- Serum ferritin was observed to be the ideal indicator to diagnose iron deplete state at an early state. When used along with MCV iron deficiency anemia can be diagnosed in cyanotic patient.
- The incidence of iron depleted state was 74% in cyanotic population.
- The incidence of iron deficiency anemia in our study was 60%.
- Incidence of congestive cardiac failure was high in patients with serum ferritin level <10ng/dl.
- Hemoglobin, hematocrit, MCHC were not useful in diagnosing iron deficiency anemia in cyanotic heart disease patients.
- There was no difference in the red cell parameters and iron status between Eisenmenger syndrome and cyanotic heart disease.
- No significant different was observed among red cell parameters between male and female cyanotic heart disease patients.

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PROFORMA

A study on iron deficiency anemia in children with cyanotic congenital heart disease

Name

Age

Sex

Provisional Diagnosis

Final Diagnosis

Cyanosis

Clubbing – Gr I/II/III/IV

H/o Iron intake present / absent

If present – duration

Signs of anemia –present / absent

Neurological complication – if any

Investigations

Hb

Hct

RBC

MCV

MCHC

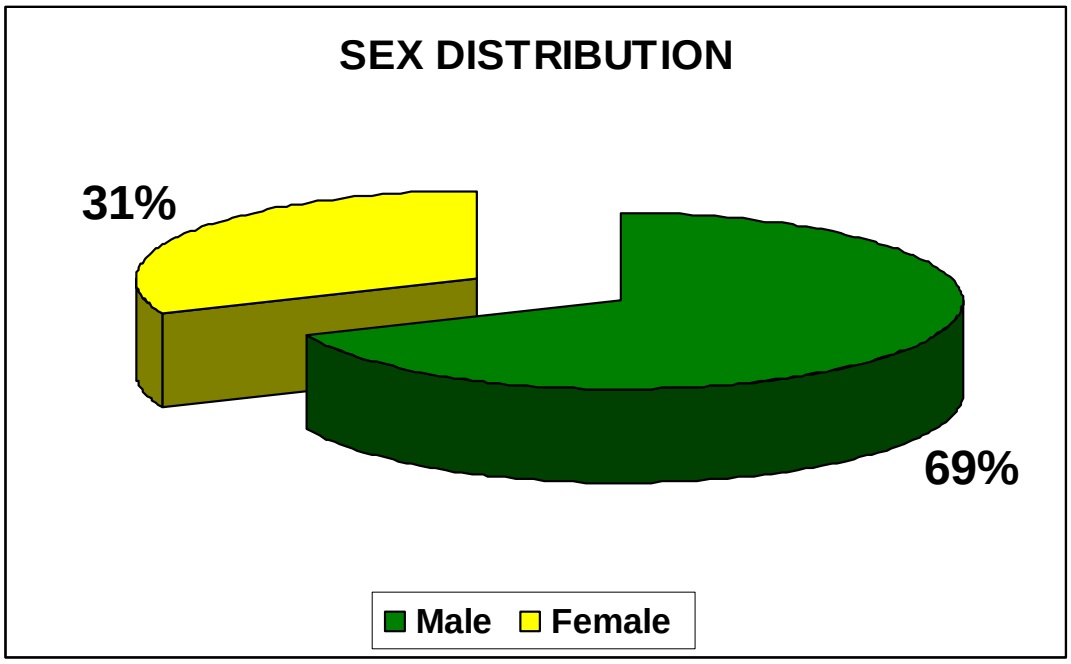
Sr. Ferritin

Sr. Iron

TIBC

MASTER CHART												
S.No.	**Age**	**Sex**	**Diagnosis**	**Hb**	**PCV**	**MCV**	**MCH**	**MCHC**	**RBC**	**Sr. Iron**	**TIBC**	**Sr.Ferritin**
1	21	M	TA	16.5	50	72.9	24	33	6.87	35	450	26
2	13	M	TAPVC	15.8	47	75.3	25.3	33.6	6.24	20	420	10
3	20	M	ToF	14.5	44	78.8	24.3	32.2	5.96	40	430	20
4	15	M	ToF	13.8	41	70	23.6	33.6	5.85	3	475	10
5	16	M	ToF	15.3	46	75.2	25	33.2	6.12	35	435	12
6	20	M	ToF	16.2	49	76	25.1	33	6.45	33	510	12
7	23	M	ToF	16.8	50	79.1	26.6	33.6	6.32	20	440	8
8	22	M	ToF	15.5	47	75.1	24.8	32.9	6.26	18	535	10
9	15	M	ToF	14.2	43	83.9	27.7	33	5.12	120	310	44
10	25	M	ToF	15	45	76.8	25.6	33.3	5.86	40	435	12
11	24	M	TAPVC	16.2	49	75.6	25	33.1	6.48	18	490	8
12	29	M	Ebstein	12.2	36.6	84.9	26.8	33.9	4.24	95	235	65
13	16	M	dorv, ps, vsd	13.8	41	70.2	23.6	33.7	5.84	38	410	15
14	12	M	dorv, ps, vsd	14.8	44	76.9	25.9	33.6	5.72	145	230	42
15	18	M	Tof, PA	13.5	41	69.7	23	32.9	5.88	28	455	12
16	13	M	ta, VSD	15.2	47	78.1	25.2	32.3	6.02	16	525	8
17	21	M	PAVM	14.8	44	75.2	25.3	33.6	5.85	48	350	22
18	19	M	vsdreversal	11.5	34	73.4	26.4	35.9	4.36	22	480	15

19	31	M	vsdreversal	16.2	49	78	25.8	33	6.28	18	465	10
20	29	M	vsdreversal	14.8	44	736	24.2	33.6	5.98	132	230	64
21	33	M	asdreversal	12.6	38	76.3	25.3	33.2	4.98	35	390	16
22	49	M	asdreversal	15.6	47	80	26.4	33.2	5.92	19	515	8
23	13	M	ecdreversal	14.8	44	80.7	27.1	33.6	5.45	26	470	14
24	18	M	ToF	15.2	45.6	77.3	25.5	33	5.45	120	235	38
25	12	F	ltga,ps,vsd	12.8	38	78.8	26.6	33.6	4.82	20	465	10
26	20	F	dorv, ps, vsd	16.2	49	72.3	24.1	33	6.72	30	470	8
27	17	F	ToF	14.8	44	75.2	25.3	33.6	5.85	148	234	60
28	13	F	ToF	11.8	35	70.1	23.8	33.7	4.96	20	515	8
29	17	F	ToF	13.5	41	79.8	24.3	32.9	5.14	45	350	18
30	13	F	ToF	12.2	37	76.4	25.2	34.3	4.84	25	465	16
31	13	F	Ctga,ps,vsd	13.2	40	67.1	22.1	33	5.96	40	210	20
32	14	F	pdareversal	14.8	44	74.6	25.1	33.6	5.9	25	435	18
33	39	F	asdreversal	15.8	47	76.8	25.8	33.6	6.12	20	475	8
34	38	F	asdreversal	12.8	38	92	31.1	33.7	4.12	20	485	8
35	16	F	vsdreversal	15.2	46	77.3	25.5	33	5.95	78	235	52


SEX DISTRIBUTION
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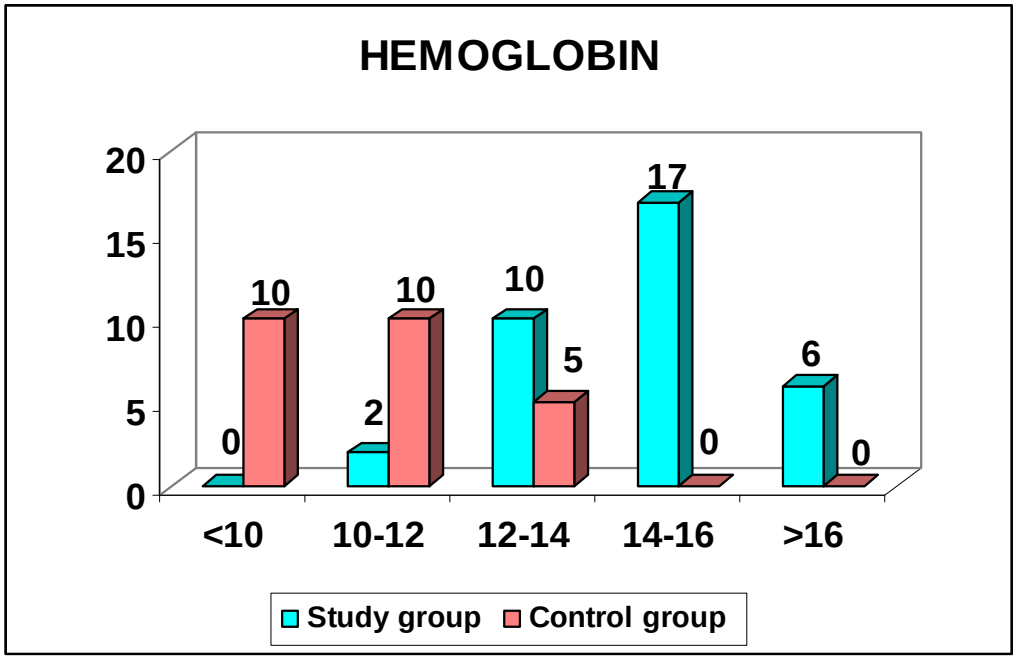
69%
Male
Female


HEMOGLOBIN
20
15
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6
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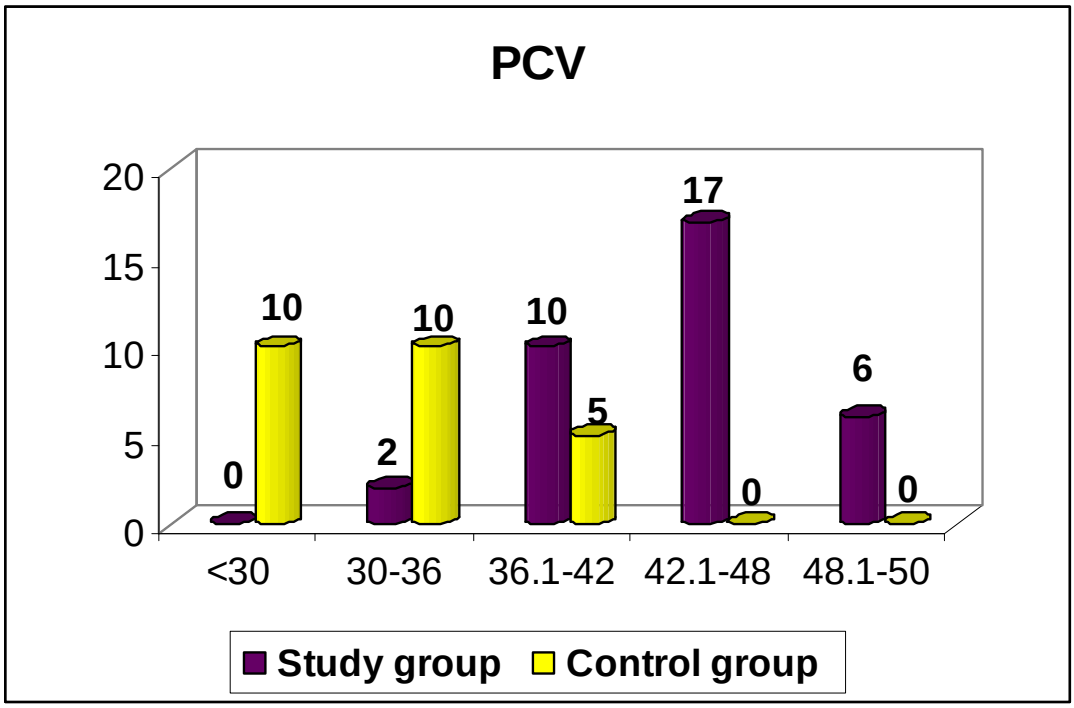
Study group
Control group


PCV
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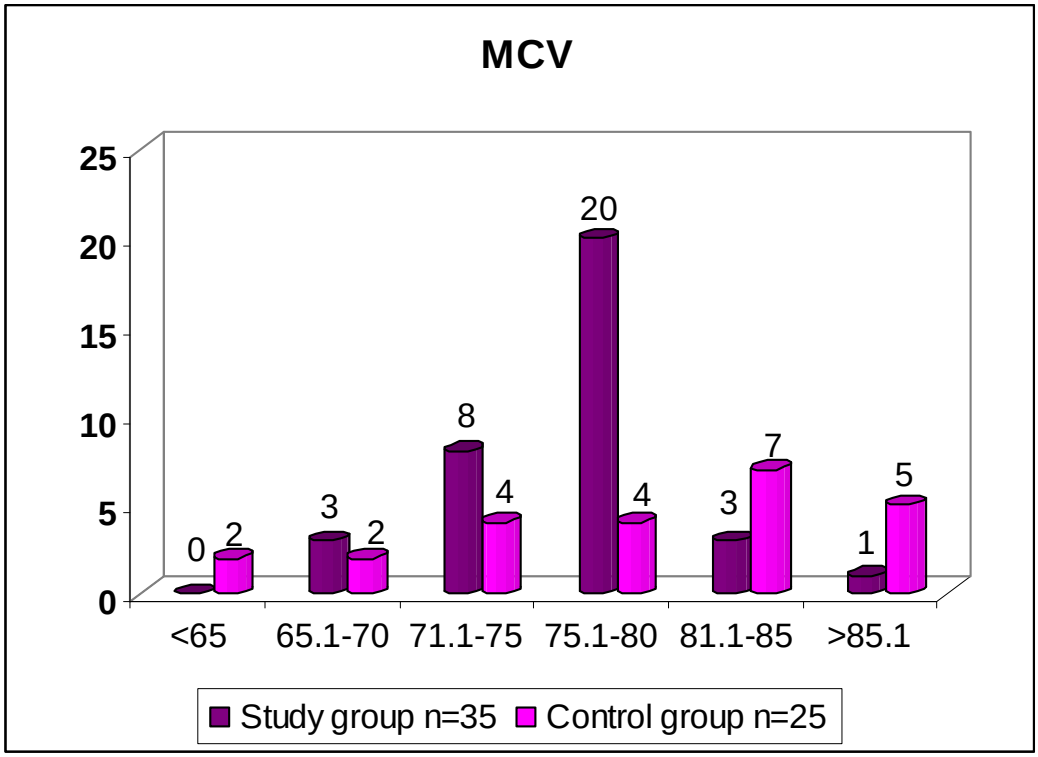
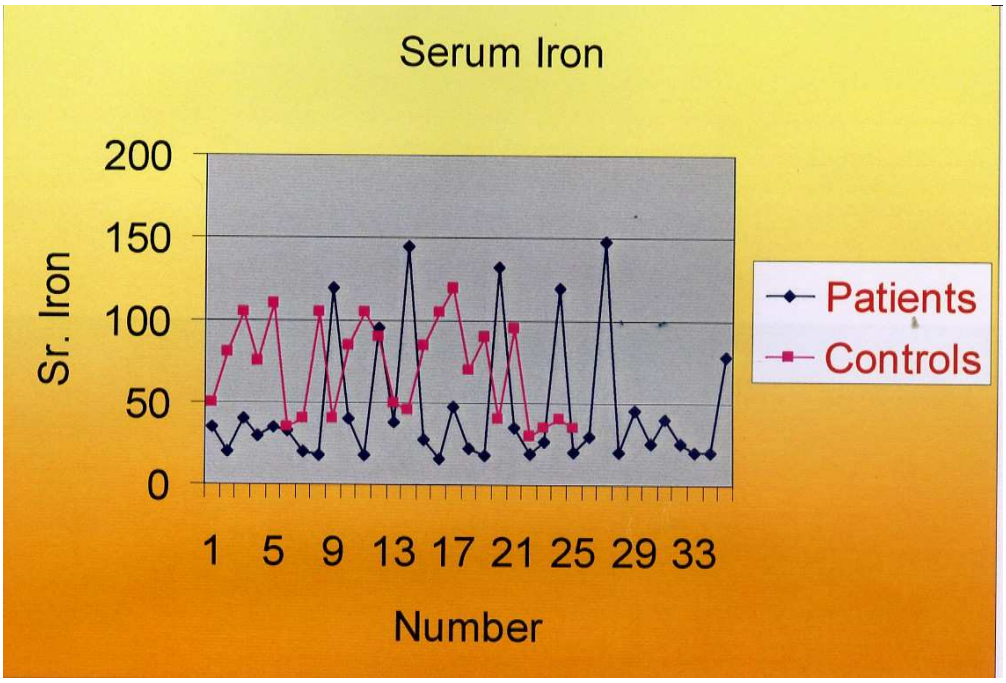
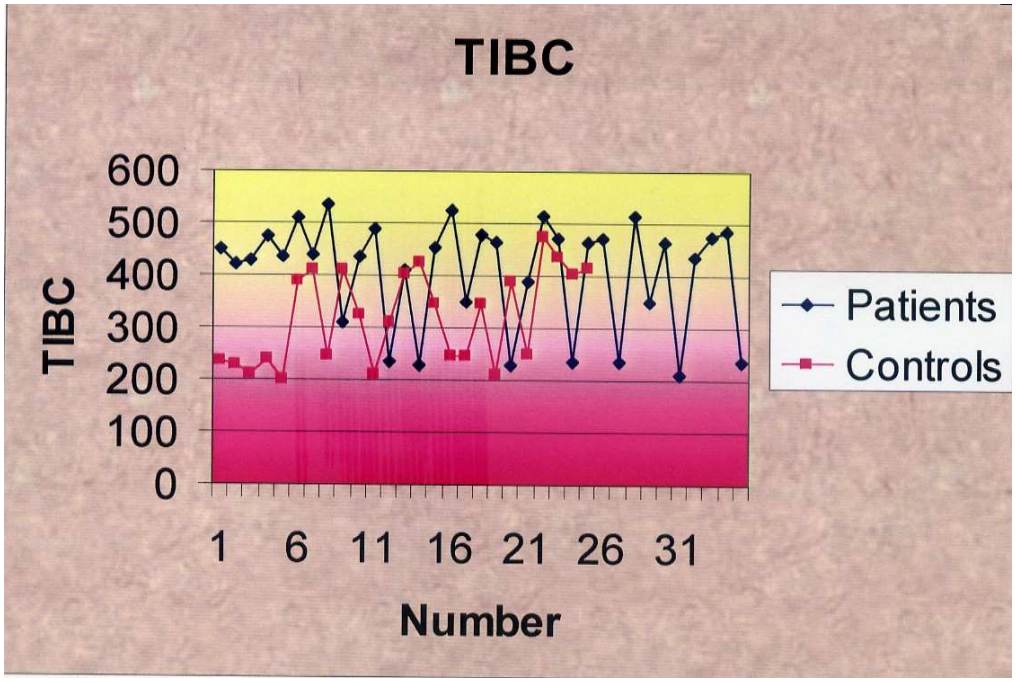
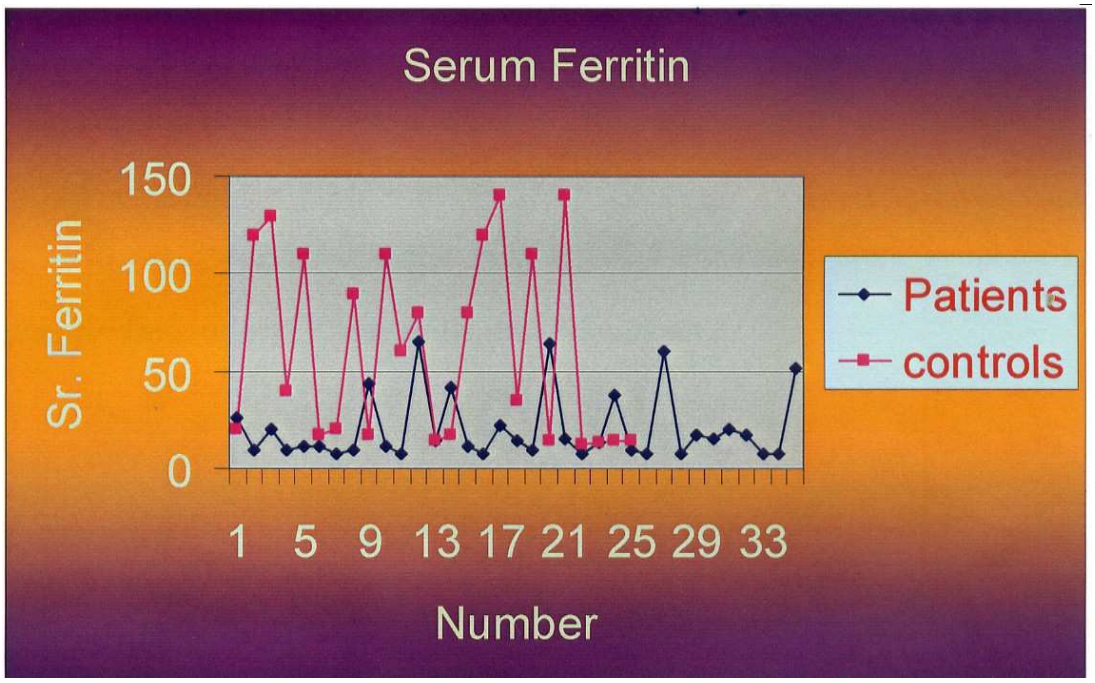
30-36
36.1-42
42.1-48
48.1-50
Study group
Control group


MCV
25
20
15
10
5
0
0
2
3
2
8
4
20
4
3
7
1
5
<65
65.1-70
71.1-75
75.1-80
81.1-85
>85.1
Study group n=35
Control group n=25


Serum Iron
Sr. Iron
200
150
100
50
0
1 5 9 13 17 21 25 29 33
Number
Patients
Controls


TIBC
TIBC
600
500
400
300
200
100
0
1 6 11 16 21 26 31
Number
Patients
Controls


Serum Ferritin
Sr. Ferritin
150
100
50
0
1 5 9 13 17 21 25 29 33
Number
Patients
controls